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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,896	METZGER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-7, 9-15, 17-19, 21-23 and 25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,16,20,24 and 30-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-10-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 8-10-05 has been entered. Claim 6 has been amended. Claims 1-45 are pending. Claims 8, 16, 20, 24 and 30-45 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8, 16, 20, 24 and 30-45 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention and is repeated for the reasons set forth in the preceding Official action mailed 2-7-05. Applicant's arguments filed 8-10-05 have been fully considered but they are not persuasive.

Applicants argue that the specification teaches administration of IL-12 protein and a TI antigen induce or enhance an immune response to the antigen in vivo, and the submitted references (exhibits A-F) show that the state of the art of IL-12-based gene therapy was not unpredictable at the time of the present invention and no undue experimentation is required for one of skilled in the art to practice the full scope of the invention claimed. Applicants further argue that the specification teaches methods of inducing or enhancing an immune response to a TI antigen in a host by administering polynucleotide encoding IL-12 protein under conditions in which the IL-12 is expressed in vivo and the presence of inoperative embodiments within the

scope of a claim does not necessarily render the claim nonenabled (amendment, p. 8-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-7-05. The specification only discloses effect of co-administration of IL-12 protein and TI antigen in stimulating or enhancing immune response to the TI antigen in a host but fails to provide data regarding whether co-administration of a TI antigen and a polynucleotide or a vector encoding IL-12 protein can stimulate or enhance humoral immune response to the TI antigen in a host. Delivery of a protein in vivo to stimulate or enhance immune response is different from delivery of a polynucleotide in vivo to stimulate or enhance immune response for therapeutic effect in vivo because the protein has been expressed in vitro, however, the polynucleotide has to be delivered to the target site and sufficient amount of protein, such as IL-12 protein, has to be expressed to stimulate or enhance immune response to TI antigen in vivo. The art of gene transfer in vivo was unpredictable at the time of the invention and one skilled in the art would not know whether sufficient amount of polynucleotide or expressed protein can be present in the targeted site to stimulate or enhance immune response as compared to TI antigen alone in a host.

The cited references Tahara (exhibit A) and Jiang (exhibit D) teach using IL-12 transfected cells to stimulate immune response in mice for anti-tumor effect. Delivery of cell in vivo to stimulate an immune response for anti-tumor effect is different from delivery of a polynucleotide in vivo to stimulate an immune response for therapeutic effects in vivo because the proteins have been expressed in the transfected cells before being released into the target site, however, the polynucleotide has to be delivered to the target site and sufficient amount of protein, such as IL-12 protein, has to be expressed to stimulate or enhance immune response in vivo. Watanabe (exhibit E) teaches intradermal injection of naked IL-12 DNA expression

plasmid and Rakhmilevich (exhibit B) delivers gold particles coated with IL-12 DNA directly to the skin overlying and surrounding target tumor site via gene gun. Kim (exhibit C) teaches intramuscular injection of IL-12 expression vector and a DNA immunogen. Okada (exhibit F) teaches intranasal immunization of a DNA vaccine with IL-12- and GM-CSF- expressing plasmids in liposomes. The specification states that "[n]on-protein antigen such as polysaccharides and lipids induce antibody response without the need for T cells and are therefore referred to as T-independent (TI) antigens (p. 1, lines 5-7). Therefore, the immune response to a TI antigen in a host is humoral immune response, i.e. antibody production, rather than cell-mediated immune response, such as CTL response. Watanabe (exhibit E), Rakhmilevich (exhibit B) and Kim (exhibit C) all show that introduction of IL-12 DNA into a host stimulate cell-mediated immune response, however, none of the references teach that introduction of IL-12 DNA into a host other than intradermal or intramuscular injection can stimulate or enhance immune response, or injection of IL-12 DNA or co-injection of IL-12 DNA and a TI antigen can stimulate or enhance **humoral immune response** in a host. Further, Kim teaches codelivery of IL-12 gene with DNA vaccine formulation for HIV-1 antigen results in **reduction** of specific antibody response, while codelivery of GM-CSF gene and said DNA vaccine results in enhancement of specific antibody response. Okada (exhibit F) reports that "[c]oinjection of vaccine plus an IL-12 expression plasmid also failed to modify HIV-specific serum Ab titers" and "[c]oadministration of IL-12 expression plasmid did not modify fecal IgA Ab levels. Again, however, a strong level of anti-V3 Ab was observed when we coadministered IL-12 plus GM-CSF expression plasmids". It appears that the type and level of Ab response can vary with the combination of a DNA vaccine (DNA for HIV-Ag) and different expression

plasmids expressing different proteins (IL-12 or GM-CSF), and coadministration of IL-12 expressing plasmid and DNA vaccine for HIV-1 does not increase or enhance humoral immune response in mice as compared to HIV-1 DNA vaccine alone. The claims encompass combination of a polynucleotide encoding IL-12 protein with various TI antigens. It was unpredictable at the time of the invention whether codelivery of various TI antigens and a polynucleotide or a vector encoding IL-12 protein can stimulate or enhance humoral immune response to the TI antigen in a host via various administration routes. Although one skilled in the art at the time of the invention know how to prepare a plasmid expressing IL-12 protein, how to administer said plasmid with a TI antigen to a host and some inoperative embodiments are allowed, however, the specification fail to provide sufficient enabling disclosure for stimulation or enhancement of humoral immune response in a host by codelivery of a polynucleotide encoding IL-12 protein and various TI antigens, and the state of the art does not render one skilled in the art to predict whether codelivery of a polynucleotide encoding IL-12 protein with a TI antigen would stimulate or enhance humoral immune response in a host. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the immune response observed by Kim and Okada is irrelevant to the claimed invention and exhibits A-F were provided to show that at the time of the invention, one skilled in the art knew how to prepare and administer a polynucleotide expressing IL-12 in combination with an antigen to induce an immune response to the antigen in vivo (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-7-05 and the reasons set forth above. The immune response by Kim and Okada

is relevant to the instant claimed invention because it shows that combination of a plasmid expressing IL-12 protein with a DNA vaccine for HIV-1 antigen does not necessarily stimulate or enhance humoral immune response in a host, however, combination of a plasmid expressing a protein other than IL-12 protein, such as GM-CSF, with either a DNA vaccine for HIV-1 antigen or a plasmid expressing IL-12 can stimulate humoral immune response in a host. If exhibits A-F cited by applicants are only to show that at the time of the invention, one skilled in the art knew how to prepare and administer a polynucleotide expressing IL-12 in combination with an antigen to induce an immune response to the antigen in vivo, then it is further evident that the specification fails to provide sufficient enabling disclosure for stimulation or enhancement of humoral immune response in a host by codelivery of a polynucleotide encoding IL-12 protein and various TI antigens, and it was unpredictable at the time of invention whether codelivery of a polynucleotide encoding IL-12 protein with various TI antigens would stimulate or enhance humoral immune response in a host.

Applicants argue that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, and the specification teaches methods of inducing or enhancing an immune response to a TI antigen in a host by administering polynucleotide encoding IL-12 protein under conditions in which the IL-12 is expressed in vivo. Applicants further cite exhibits A-F and argue that the claimed invention is routine experimentation and no undue experimentation is required (amendment, p. 12-14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 2-7-05 and the reasons set forth above. The immune response to a TI antigen in a host is humoral immune response, i.e. antibody production, rather than cell-mediated immune response, such as

CTL response. The statement on second paragraph, page 7 of the Official action mailed 2-7-05, is to indicate that the prior art only teaches intratumoral or intramuscular injection of IL-12 DNA into a host to stimulate cell-mediated immune response, however, none of the references teach that introduction of IL-12 DNA into a host other than intradermal or intramuscular injection can stimulate or enhance immune response, or injection of IL-12 DNA or co-injection of IL-12 DNA and a TI antigen can stimulate or enhance **humoral immune response** in a host. The 35 U.S.C. 112 first paragraph rejection is a full-blown enablement rejection (see Official action mailed 2-7-05, bridging p. 2-3, p. 8, first paragraph). The specification fails to provide sufficient enabling disclosure for stimulation or enhancement of humoral immune response in a host by codelivery of a polynucleotide encoding IL-12 protein and various TI antigens via various administration routes, and it was unpredictable at the time of invention whether codelivery of a polynucleotide encoding IL-12 protein with various TI antigens would stimulate or enhance humoral immune response in a host.

Conclusion

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER